Interim Milestones to Complete the First Goal of the National Alzheimer's Plan by 2025

*Includes cross references with corresponding recommendations from **Alzheimer's Disease Research Summit 2012***

Years	Milestones in Research	Milestones in Regulatory Review	Interim Benefits to General Population
2012-2015	• Adoption of National IRB reduces trial duration (S3B8[i];S6B7[ii]) • International Infrastructure for academic/industry interface and data sharing accelerates research (S1B8[iii];S6B4[iv]) • Validated biomarker for MCI due to AD (S1B6[v];S3B5[vi]) • Large scale clinical trial registry launched (S3B3[vii]) • Secondary prevention trials launched (S3B1[viii]) • Validated cognitive endpoint for MCI due to AD (S3B4[x]) • Large scale community-based longitudinal cohort speeds trial enrollment (S3B3[xii])	• FDA adaptive trial model for AD is adopted in industry trials (S2B10[ix]) • Qualified biomarker for MCI due to AD incorporated into industry trials[xi] • Qualified cognitive endpoint for MCI due to AD incorporated into industry trials[xi]	
2016-2020	• Established pathological pathway for AD including genomics for accurate target identification in clinical trials (S1B1[xiii];S1B2[xiv]) • Validated biomarker for asymptomatic AD and disease progression (S3B5[xv]) • Validated cognitive endpoint for asymptomatic AD (S4B3[xvi];S5B3[xvii]) • Active implementation of secondary prevention into clinical communities in asymptomatic AD (S5B7[xviii])	• New FDA approved treatment to ameliorate symptoms of dementia due to AD [xi] • Qualified surrogate endpoints for autosomal AD [xi] • Qualified biomarker for asymptomatic AD and monitor disease progression[xi] • FDA approved Dx for MCI due to AD[xi] • FDA approved treatment to delay Alzheimer's dementia in people with MCI due to AD[xi]	• Approved treatment begins to delay chronic disability of AD • Recently approved treatment reduces rate of nursing home placement • Dx for MCI due to AD leads to earlier detection and effective management • New treatment leads to secondary prevention of AD at MCI stage

Years	Milestones in Research	Milestones in Regulatory Review	Interim Benefits to General Population
2021-2025	• Active implementation of secondary prevention into clinical communities in asymptomatic AD (S5B7[xix])	• FDA guidance on cognitive endpoint for asymptomatic AD[xi] • FDA approved Dx for asymptomatic AD[xi]	• Recently approved treatment for MCI due to AD further reduces nursing home placement • Dx for asymptomatic AD leads to earlier detection and effective management
	• Delay MCI in people with asymptomatic AD	• FDA approved treatment to delay MCI due to AD in people with asymptomatic AD[xi]	• Secondary prevention/effective treatment of AD at an asymptomatic stage

NOTE: Each endnote cites a recommendation from Alzheimer's Disease Research Summit (ADRS) 2012 [http://www.nia.nih.gov/announcements/2012/05/alzheimers-research-summit-may-14-15-2012]. Citations are made using the format S#B#, where S# refers to the Session number, and B# refers to a particular bulleted recommendation from that session. For instance, S3B4 would refer to the fourth bulleted recommendation from Session 3. These recommendations are available directly at: http://www.nia.nih.gov/newsroom/announcements/2012/05/alzheimers-disease-research-summit-offers-research-recommendations.

[i] S3B8: "Support broad infrastructure changes that will accelerate and improve the efficiency of prevention initiatives, including the formation of a national centralized Institutional Review Board for multi-center Alzheimer's disease trials and the development of agreements for data sharing of de-identified data from both placebo and treatment arms via public databases."

[ii] S6B7: "Develop a National Institutional Review Board for Alzheimer's disease studies accessible to both public and private funding research organizations."

[iii] S1B8: "Enable rapid sharing of new data via web-based resources with the capacity to store large and diverse datasets (such as data about clinical phenotypes, genetics, epigenetics, proteomics, and metabolomics) that can be used for testing different models or hypotheses at the computational level."

[iv] S6B4: "Data sharing (with standardized ontologies and metadata)."

[v] S1B6: "Develop robust biomarkers that can feasibly be obtained in large cohorts of volunteers, including metabolic signatures to develop and validate diagnostic, prognostic, and surrogate biomarkers for Alzheimer's disease and biomarkers for disease subtypes."

[vi] S3B5: "Optimize biomarkers for detecting and monitoring the progression of Alzheimer's disease, and focus particularly on standardization. These biomarkers will be used to elucidate the temporal trajectories over the course of preclinical and prodromal Alzheimer's disease, to assess the proximity to onset of clinical symptoms, and to predict long-term clinical response to treatment."

[vii] S3B3: "Expand large-scale registries and natural history cohorts of healthy individuals from early midlife to late-life, as well as individuals with subjective and/or objective cognitive impairment and use the data generated to inform clinical trial design. These cohorts should be population-based and should oversample underrepresented ethnic minorities and groups with lower education."

[viii] S3B1: "Initiate treatment trials in asymptomatic, at-risk individuals (e.g., individuals at risk genetically, older adults positive for biomarkers for Alzheimer's disease) using uniform biomarkers and cognitive outcomes, informed by data from Alzheimer's disease trials using patients with more advanced disease."

[ix] S2B10: "Provide an expedited review track for applications focused on drug discovery, preclinical, and clinical drug development for Alzheimer's disease to mitigate difficulties with intellectual property and commercialization issues that are imposed by the current lengthy review/grant cycle at the NIH. Establish multi-disciplinary review panels with adequate expertise to evaluate all aspects of translational research."

[x] S3B4: "Develop, validate, and standardize sensitive neuropsychological and other clinical and behavioral measures to detect and track the earliest clinical manifestations of Alzheimer's disease and to predict long-term clinical and functional outcomes. These measures should be sensitive to change and capture the variability in cognitive function that may be an important predictor of treatment response."

[xi] While not directly referenced in ADRS 2012 recommendations, this milestone is a straightforward and critical milestone in the translation of research advances to full the purposes of PL 111-375 (http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf) and Goal 1 and corresponding strategies in the National Plan to Address Alzheimer's Disease (http://aspe.hhs.gov/daltcp/napa/NatlPlan.shtml).

[xii] S3B3: "Expand large-scale registries and natural history cohorts of healthy individuals from early midlife to late-life, as well as individuals with subjective and/or objective cognitive impairment and use the data generated to inform clinical trial design. These cohorts should be population-based and should oversample underrepresented ethnic minorities and groups with lower education."

[xiii] S1B1: "Intensify scientific efforts to deepen the understanding of the complex pathobiology of Alzheimer's disease, and diversify target identification to better address the multifactorial nature of the disease. These efforts should include the use of systems biology approaches and tools, as well as cutting-edge stem cell technology."

[xiv] S1B2: "Develop a better systems-level understanding of how the many discoveries that have already been made (e.g., genetic, pathological, biochemical, radiological, neuropsychological) and the contributory factors that have already been identified (e.g., Ab, tau, apoE4, a-synuclein, TDP-43, aging, proteostasis failure, mediators of inflammation, comorbidities) are related mechanistically."

[xv] S3B5: "Optimize biomarkers for detecting and monitoring the progression of Alzheimer's disease, and focus particularly on standardization. These biomarkers will be used to elucidate the temporal trajectories over the course of preclinical and prodromal Alzheimer's disease, to assess the proximity to onset of clinical symptoms, and to predict long-term clinical response to treatment."

[xvi] S4B3; "The optimal therapy for Alzheimer's disease may involve the use of drug combination cocktails and require different composition of these cocktails at different stages of the illness. To facilitate the development of effective combination therapies, develop translational workgroups that include experts in network biology and network pharmacology."

[xvii] S5B3: "Initiate rigorously designed clinical trials in asymptomatic and cognitively impaired older adults to establish the effectiveness of physical exercise, cognitive training, and the combination of these interventions for Alzheimer's disease treatment and prevention."

[xviii] S5B7: "Invest in research to develop technologies that promote prevention and treatment trials, clinical care, caregiver support, and in-home monitoring."

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